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CERTIFICATE

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I hereby certify that annexed is a true copy of the Provisional Specification as filed on 27 October 1999 with an application for Letters Patent number 500630 made by BOMAC LABORATORIES LTD.

Dated 23 August 2000.

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Neville Harris
Commissioner of Patents



500630

PATENTS FORM NO. 4

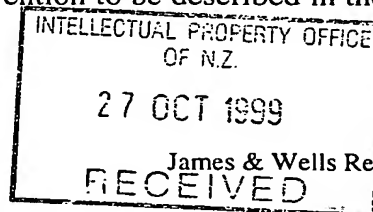
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PATENTS ACT 1953
PROVISIONAL SPECIFICATION

**IMPROVEMENTS IN AND RELATING TO ANTI-INFLAMMATORY
COMPOSITIONS AND OTHERS**

I/WE Bomac Laboratories Limited, a New Zealand company of corner Wiri Station Road and Hobill Avenue, Manukau City, Auckland, New Zealand, do hereby declare this invention to be described in the following statement:

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IMPROVEMENTS IN AND RELATING TO ANTI-INFLAMMATORY COMPOSITIONS AND OTHERS

TECHNICAL FIELD

5 The present invention is directed to compositions exhibiting pharmaceutical activity and which include two or more components selected from: green lip mussel extract, *pinus radiata* bark extract, and shark cartilage. Preferred embodiments of the invention comprises a sustained slow-acting composition which, when continually administered, exhibit anti-inflammatory effects though various embodiments may also exhibit analgesic effects, gastro-protective effects, a reduction in host-cell damage
10 associated with inflammation, and may reduce cancerous tumours through antiangiogenesis. Varying embodiments may exhibit a number, or all, of these effects to varying degrees depending upon the degree and balance of synergism resulting from the selected components and ratios.

BACKGROUND ART

15 The present invention was developed with the needs and problems associated with domestic animals in mind. In particular, domestic pets receive significantly more attention from humans than domesticated commercial species (e.g. livestock). The care and attention lavished on domestic pets also means that they tend to live to a significantly greater age than most commercially bred species and are thus more likely
20 to exhibit the problems associated with old age. Such problems include cancer, and debilitating degenerative diseases.

In addition, animals are also susceptible to inflammation associated with various causes such as tissue damage or injury, and as for their human counterparts, some animals may also experience gastro-intestinal irritation from commonly used anti-
25 inflammatories. As many domesticated pets are regarded by owners as family

members, owners are often keen to address the various maladies that their pets exhibit

However, in most cases the solution is a curative remedial action after the problem has presented itself. While this may be effective for temporary afflictions such as acute infectious inflammation, longer term afflictions such as cancer and debilitating degenerative ailments have associated degenerative or other effects which are not usually fully reversible and quite often any remedial action is merely to attempt to control the further spread of the affliction, or to ameliorate its effects on the animal. In some instances a partial improvement may be obtained, though there are problems associated with addressing an affliction after it has firmly established itself. As for humans, early diagnosis is often associated with a better prognosis for recovery or control.

Accordingly, a number of afflictions such as cancer or debilitating degenerative ailments (e.g. arthritis) may be more effectively controlled if preventative measures are taken. For instance there is evidence indicating that cartilage protecting agents may help protect against the occurrence of degenerative joint diseases and associated complaints. While there are varying forms of joint diseases, in general the complaint is accompanied by degeneration of cartilagenous material at the joints. The sooner action is taken against such degeneration, then the less the effects of the complaint will be. Thus, while an animal may still remain susceptible to joint related afflictions, preventative measures may protect against development of the complaint to any appreciable degree.

Similarly, inflammation at the joint is a factor in some degenerative joint diseases and thus some protection may also be provided by preventing inflammation in affected areas.

There are also a number of different types of cancers, though in particular the present invention is more focussed on those accompanied by tumourous growths. In many

instances these tumours may be relatively benign though any tumourous growth is potentially serious. Again there is a link between early prognosis and recovery or effective control of the cancer and thus any preventative measure which can hinder the early growth or development of tumours will be of use.

- 5 For most animals, there is a limited number of products available which can be safely administered to afford a preventative or curative action towards these types of afflictions. Most animal remedies are based on pure chemicals for addressing a particular diagnosed chemical imbalance. Many of these contain side effects, and even for those that don't, it is generally not a recommended practice for their regular
10 continued administration.

For domestic pets, there have been on-going improvements in food formulations, though again the primary emphasis has been on presenting a tailored balance of nutrients for different animals. A number of more recent formulations have addressed the elimination of problem components, or have altered the foodstuff characteristics to
15 counter known problems in pets – for example, altering the pH of certain pelletised cat foods to avoid urinary tract problems in adult cats. Most focus on various vitamins and minerals and may also increase or reduce specific amino acids present in the foodstuff. Some products have become quite specialised and one American product is specifically formulated for dogs undergoing chemotherapy, and includes high levels of
20 n-3 fatty acids, which inhibit tumour growth.

However, there is a general need for a composition which can be administered on a regular basis to both healthy and afflicted animals and which can address one or more of a number of known, common, problems such as indicated above. Accordingly it is one aspect of the present invention to provide a composition, in a dosage form, or an
25 alternate form, which can be administered regularly and in with relative safety to most domesticated pets, and particular mammalian species. At the very least, it is an object of the present invention to provide the public with a useful alternative to what is

currently available.

Further aspects and advantages of the present invention will become apparent from the ensuing description which is given by way of example only.

DISCLOSURE OF INVENTION

5 According to one aspect of the present invention there is provided a composition for administration to animals which includes the combination of:

(a) at least one anti-inflammatory agent selected from the group comprising
i) green-lipped mussel extract (GLME) and/or a pharmacologically active
green lipped mussel extract, and

10 ii) shark cartilage and/or pharmacologically active shark cartilage extract with

(b) at least one enhancing agent selected from the group of:

i) Enzogenol™, and/or equivalent bark extract, and

ii) shark cartilage;

15 and wherein for a composition including just one member from each group, the selected members must be different.

According to one aspect of the present invention there is provided a composition for addressing degenerative joint ailments, for administration to animals which includes the combination of:

20 (a) shark cartilage and/or pharmacologically active shark cartilage extract with

(b) at least one enhancing agent selected from the group of:

i) Enzogenol™, and/or equivalent bark extract, and

25 ii) green-lipped mussel extract (GLME) and/or a pharmacologically active green lipped mussel extract.

According to another aspect of the present invention there is provided a composition, substantially as described above, which includes an antioxidant.

According to another aspect of the present invention there is provided a composition, substantially as described above, in which the antioxidant comprises vitamin E.

- 5 According to another aspect of the present invention there is provided a composition, substantially as described above, which includes deer velvet.

According to another aspect of the present invention there is provided a composition, substantially as described above, which includes additional glycosaminoglycans than those present in the selected anti-inflammatory or enhancing agents.

- 10 According to another aspect of the present invention there is provided a composition, substantially as described above, which includes additional chondroitin sulphate than that present in the selected anti-inflammatory or enhancing agents.

- According to another aspect of the present invention there is provided a composition, substantially as described above, which includes sufficient GLME or mussel extract to
15 provide gastro-intestinal protection against irritation by other components in the composition.

According to another aspect of the present invention there is provided a composition, substantially as described above, used as a carrier for medicaments.

- According to a further aspect of the present invention, there is provided a
20 composition, for anti-inflammatory use, for administration to animals which includes the combination of:

- (a) at least one anti-inflammatory agent selected from the group comprising
i) green-lipped mussel extract (GLME) and/or a pharmacologically active green lipped mussel extract, and

ii) shark cartilage and/or pharmacologically active extract thereof; with

(b) at least one enhancing agent selected from the group of:

i) Enzogenol™, and/or equivalent bark extract.

According to another aspect of the present invention there is provided a composition,
5 for anti-inflammatory use, substantially as described above, which includes additional
anti-oxidants, and preferably vitamin E.

According to a further aspect of the present invention there is provided a composition,
for use in addressing degenerative joint complaints, for administration to animals
which includes green-lipped mussel extract (GLME) and/or a pharmaceutically active
10 green lipped mussel extract, in combination with shark cartilage.

According to another aspect of the present invention there is provided a composition,
for use in addressing degenerative joint complaints, substantially as described above,
which includes additional anti-oxidants, and preferably either or both of (i) vitamin E
and (ii) Enzogenol™ and/or an equivalent bark extract.

15 According to another aspect of the present invention there is provided a composition,
substantially as described above, as a dosage form for oral administration.

According to another aspect of the present invention there is provided a composition,
substantially as described above, in the form of a pill, tablet, or capsule.

According to another aspect of the present invention there is provided a composition,
20 substantially as described above, incorporated into an animal food product.

According to a further aspect of the present invention there is provided the use of any
two or more of:

i) green-lipped mussel extract (GLME) and/or a pharmacologically active
green lipped mussel extract,

25 ii) shark cartilage and/or pharmacologically active shark cartilage extract; and

iii) Enzogenol™, and/or equivalent bark extract.

in the preparation of a composition for use in addressing any one or more of:

- a) inflammation;
- b) degenerative joint complaints;
- 5 c) other cartilagenous degeneration;
- d) gastrointestinal sensitivity or irritation;
- e) cancerous tumours;

The present invention has been developed with the needs of domesticated pets, and primarily mammalian species, in mind though it is also envisaged that the present invention is applicable to commercially bred species. However, while tablets or foodstuffs may be regularly administered or fed to pets or stabled animals, the problems associated with regular administration to sheep, cattle, and other livestock, may preclude regular use of the present invention with those species. However this does not mean that the present invention is detrimental to, and therefore cannot be administered to, such species or animals.

Preferred embodiments of the present invention focus around the use of three components, or equivalents thereof. These comprise green lipped mussel extract (GLME), shark cartilage and ENZOGENOL™. Each of these components alone is known to exhibit a number of useful properties, though it has been found that varying combinations of these components can yield a significant improvement in the effectiveness of these components alone, and also render the resulting combination useful for addressing a number of complaints.

For instance, green lipped mussel extract (GLME) comprises extractions from the shellfish species *perna canaliculus*, a mollusc found on the shores of New Zealand. This has been found to contain a number of components exhibiting anti-inflammatory activity and includes small amounts of glycosaminoglycans which have been shown to be beneficial for maintaining the integrity of cartilage and bone. Accordingly, green

lipped mussel extract has been used for alleviating arthritic complaints, including degenerative joint diseases.

Green lipped mussel extra (GLME) where used in various embodiments of the present invention is preferentially that obtained from extraction processes from live, or recently killed mussels. Procedures such as outlined in granted patents to the inventor Stuart J McFarlane may be followed, though the product may preferentially be obtained from McFarlane Laboratories NZ Ltd., of New Zealand.

The same inventor has also pursued further patent applications directed to extracting specific targeted compounds from green lipped mussels, and re-combining or using these in other preparations. An example is the disclosure of US 4,455,298 (NZ 188489). Such extracts are also considered to be among acceptable substitutes for green lipped mussel extract (GLME) for use in the present invention.

Shark cartilage has also been used by persons suffering from disorders such as cancer and arthritis and there it appears that it is useful in addressing these complaints. Identified active components include chondroitin sulphate, and glycosaminoglycans. Various shark cartilage products may be used, though preferentially include or retain active quantities of these components.

The third component which has been mentioned is ENZOGENOL TM, a proprietary composition manufactured by Enzo Nutraceuticals Limited, of Christchurch, New Zealand, and comprises an extract from the bark of *Pinus radiata* which is rich in anti-oxidants. There is evidence establishing that oxidant and free radical damage can be addressed by this formulation. Both oxidant and free-radical damage have been shown to be involved in both premature ageing, and in particular, joint disease. Equivalent products to ENZOGENOL TM may be substituted, though the preference is for this product.

As previously indicated, it has been indicated that a significant useful improvement can be made by combining two or more of the three listed components. The selected combination will have some effect on the focus and activity of the resulting combination, and this will become more apparent from the following description.

- 5 - One possible combination is GLME with shark cartilage. This combination is of use as an anti-inflammatory, though in particular is useful for addressing arthritic complaints and degenerative joint problems. For instance, GLME includes glycosaminoglycans which help protect cartilage and bone. GLME also exhibits an anti-inflammatory effect. Most arthritic complaints and degenerative joint disorders
10 are known to involve an associated inflammation in the joint region and thus GLME's demonstrated effectiveness in these type of disorders have been at least partly attributable to the anti-inflammatory characteristics.

Shark cartilage contains higher levels of glycosaminoglycans which augments the cartilage protective effects of GLME alone. This is further augmented by the presence
15 of chondroitin sulphate, another cartilage protecting component. The collagen also present in shark cartilage further enhances the effectiveness of the combination.

Shark cartilage also possess some antiangiogenetic properties which also affords the combination and additional properties in addressing cancer tumour formation. It is also considered that the same property may also further enhance the ability of the
20 combination to address, both preventatively, and curatively (to varying degrees) joint and cartilage problems – particularly mobility related ailments.

ENZOGENOL™, or equivalent bark extracts, may also be combined with either or both of GLME and shark cartilage. Both GLME and shark cartilage possess anti-inflammatory properties. The combination with ENZOGENOL™, with its anti-oxidant
25 and anti-free radical properties, enhances the usefulness of these anti-inflammatories in addressing a number of disorders, and preventing the formation of other problems. For

instance, inflammation is generally the consequence of a defensive action of the body and in some instances is accompanied by a significant amount of oxidants in the inflamed regions. These oxidants often include nitrous oxide, varying peroxides and a number of other substances which exhibit a strong localised anti-microbial effect.

- 5 However, the effectiveness of their action is not always confined to foreign bodies. These oxidants produced by the body are also known to exhibit a negative effect on the host's own cells, and it is known that some oxidant species can disrupt host cell DNA sequences. Current theories consider this to be the first transformational change to occur in a number of forms of cancer, and thus addressing this problem will represent a
10 preventative technique towards the establishment of a number of forms of cancer.

- Anti-oxidants, such as those provided in ENZOGENOL™, can reduce damage to the host's own cells, but without any significant decrease in the effectiveness of remaining oxidants in addressing microbial invaders and other foreign material. In some respects the anti-oxidants may be considered to have a regulating effect and tend to mop up
15 excess oxidants which have been produced beyond the actual needs of the body.

Accordingly, the combination of an anti-oxidant such as ENZOGENOL™, or equivalents thereof, with an anti-inflammatory, produces a substantially enhanced useful overall effect in reducing not only the amount of inflammation, but negative side effects associated with inflammation.

- 20 Further, the reduction in likelihood of an oxidant induced cancer transformation, coupled with the antiangiogenetic properties of shark cartilage renders this a useful combination for reducing the probability of cancer formation.

- Further, it will be appreciated that the combination of all three can yield a highly useful product which can help simultaneously address a number of afflictions which
25 affect animals, and which become more prevalent in older animals.

Another anti-oxidant which may be used in varying embodiments of the present invention is vitamin E. Other anti-oxidants are also known, and both these and/or vitamin E may be used in varying embodiments including these combining GLME with shark cartilage. However, preferred embodiments would include ENZOGENOL™
5 as the preferred anti-oxidant of choice, though it should be also appreciated that not all uses of varying embodiments will focus on inflammation and its side-effects, and thus lower levels of additional anti-oxidant activity may be provided, if at all.

As can be appreciated, the varying combinations which have been described provide enhanced activity and properties over the individual components. The result is a range
10 of embodiments which may be used in a number of similar roles, but which may exhibit slightly enhanced activity in one role over another.

Some of these components possess other useful properties which may extend the usefulness of various combinations. For instance, GLME is known to be useful in preventing, alleviating, or treating gastro-intestinal irritation. Accordingly,
15 compositions of the present invention which include GLME may also be used as a carrier for, or as part of, compositions containing irritant substances just as GLME alone is used in such a role. This further extends the usefulness and flexibility of embodiments of the present invention.

For instance, many current fast-acting anti-inflammatories are irritating to the stomach.
20 While embodiments of the present invention generally include sufficient anti-inflammatory activity, when administered over sustained periods, to preclude the use of most existing pharmaceutical anti-inflammatories, there may be instances where the user may wish or need to include one of these existing faster acting compounds. Including such a substance in such embodiments of the present invention may not only
25 reduce the amount of the added anti-inflammatory which needs to be included, but the counter irritant effects of GLME can help reduce the side-effects from the administration of an added anti-inflammatory which may cause irritation.

There are a number of other pharmaceuticals which exhibit irritant properties, and the co-administration, or co-compounding, of embodiments of the present invention with those substances is also a technique within the scope of the present invention. In particular, embodiments of the present invention may find use for administration
5 during chemotherapy which tends to have a number of significant negative side effects.

Embodiments of the present invention may also include other substances which are known to have a beneficial effect. One such substance is deer velvet for which a large amount of anecdotal, but little clinical, evidence exists of its effectiveness. The little clinical work which has been performed suggests that deer velvet administered orally
10 can address problems associated with high blood pressure, as well as having both immuno-stimulatory and anti-inflammatory properties. The inclusion of deer velvet would therefore augment such properties already existing in various embodiments of the present invention.

It is also envisaged that varying embodiments may also include manganese ascorbate and/or S-adenosylmethionine (aka S-adenosyl-L-methionine, 1,4 butane disulfonate).
15 This latter compound is also known to promote joint mobility, while the former is involved in the biosynthesis of glycosaminoglycans. These can enhance the action of other components in preferred embodiments of the invention addressing debilitating joint ailments.

As mentioned previously, the present invention may take varying forms. It is envisaged that a common form of the invention is as an oral dosage form. This may be as a pill, tablet, capsule, etc. Liquid formulations may also be produced, as may other types of solid formulations. In particular, an animal foodstuff is envisaged. Each of these different forms may be prepared according to standard existing techniques, and
20 which include the components of the various embodiments of the present invention.
25

BEST MODES FOR CARRYING OUT THE INVENTION

Example 1: Compositions for adult dogs

This comprises a tablet (or similar dosage form) or dietary foodstuff which includes green lipped mussel extract in combination with shark cartilage. Ideally, the composition also includes a range of vitamins and trace minerals in a balanced proportion, ideal for targeted animal range. Different embodiments may contain different ratios, depending upon the size, type, or age of the animal.

Example 1a: Constituents

In this embodiment, a dosage form, which may take the form of a pellet, capsule or tablet etc, may contain:

Green Lipped Mussel Extract	50 – 200 mg
Shark cartilage	50 – 200 mg
Vitamin mix	200 ± 200 mg

Which may, for example, consist of:

15	Vitamin A	2000-3000 iu
	Vitamin D3	300-500 iu
	Vitamin E	20-30 iu
	Vitamin K3	0.5-0.75 mg
	Thiamine (Vitamin B1)	1-1.5 mg
20	Riboflavin	2-3 mg
	Pyridoxine	0.5-0.75 mg
	Panthenic acid	2-3 mg
	Niacin	7-10.5 mg
	Biotin	0.1-0.75 mg
25	Vitamin B12	22-150 µg
	Folic acid	0.1-0.15 mg
	Iron	12-20 mg
	Copper	1.5-2.5 mg

5	Cobalt	0.25-0.4 mg
	Manganese	3-5 mg
	Zinc	25-40 mg
	Iodine	0.5-0.75 mg
	Selenium	0.075-0.125 mg
	Calcium	10-20 mg
	Manganese ascorbate	optional
	S-adenosylmethionine	optional

10 The dosage form may also be incorporated into a food product, such as a pellet, which can be administered for consumption by the animal. Such dosage forms could also be seeded throughout pelletised animal foods – lower dosage forms may be prepared for such applications.

For the embodiment above, a typical suggested once daily dosage is:

15	up to 15 kg	1 tablets
	15 – 30 kg	2 tablets
	over 30 kg	3 tablets

This example is illustrative only. The vitamin mix is illustrative of a typical balance for adult dogs, but can be varied (and components added or eliminated) in different embodiments for other species and ages.

20 Example 2

This comprises a dosage form combining GLME with an anti-oxidant, and is of particular use for preventing or addressing inflammation.

In this embodiment a typical dosage form may contain:

25	Green lipped mussel extract	50 – 200 mg
	ENZOGENOL™	5 ± 2 mg
	Vitamin mix (see example 1a)	200 ± 200 mg

As for Example 1, the dosage form may take different forms, including capsules, tablets, pellets, and even liquid forms. Liquid forms would generally include an

acceptable carrier, and may include inert oils such as comestible vegetable oils, and fish oils.

Example 3

- 5 This example combines shark cartilage with ENZOGENOL™. While this combination is useful for addressing inflammation, it is directed more to the prevention, and/or addressing arthritic complaints and degenerative joint diseases and afflictions.

In this embodiment the dosage form may contain:

	Shark cartilage	50 – 200 mg
	ENZOGENOL™	2 – 10 mg
10	Vitamin mix (see example 1a)	200 ± 200 mg.
	preferably including adenosylmethionine and manganese ascorbate.	

Dosages and varying dosage forms, are as for the preceding examples.

Example 4

- 15 This embodiment includes deer velvet in addition to the compositions of any of the preceding examples. To a formulation as described in any of examples 1 through 3, there is also included deer velvet in the amount of 25 ±10 mg. Preferably this is dried deer velvet, which has been prepared by a method avoiding substantial degradation of included natural components.
- 20 Dosing and administration is as per Example 1 herein.

Example 5: for older or arthritic animals, or animals exhibiting mobility problems

These embodiments may also be in dosage forms, or foodstuffs. This range of embodiments are targeted at older animals, and particularly those that may be showing joint problems or arthritis.

- 25 These embodiments combine green lipped mussel extract with shark cartilage or extracts thereof. Ideally, the shark cartilage, or any extract thereof, should include glycosaminoglycans. These two active components act as powerful anti-

inflammatories, and provide anti-inflammatory action over the use of the green lipped mussel extract alone.

Optionally but ideally also, deer velvet or extract thereof is included in the these formulations.

- 5 Ideally also, these embodiments will also include ENZOGENOL (proprietary formulation of anti-oxidants).

Example 5a: Constituents

Each tablet contains:

10	Green Lipped Mussel Extract	175 ± 75 mg
	Deer Velvet	25 ± 10 mg
	Shark Cartilage	100 ± 50 mg
	ENZOGENOL (™)	5 ± 2 mg
	Vitamin mix (see example 1a)	200 ± 200 mg

Suggested once daily dosage as per example 1a.

- 15 May be fed in conjunction with Example 1a formulation. Can be administered directly into the mouth or added to the food.

Example 6: for cats

- 20 The preferred embodiment for cats will include green lipped mussel extract. This acts in the role of an anti-inflammatory to improve mobility, as well as relief from sore and arthritic joints. Again, preferred embodiments of this range will also include a balanced range of vitamins and trace minerals for cats.

Example 6a: Constituents

Each tablet contains:

	Green Lipped Mussel Extract	175 ± 75 mg
	Either or both of:	
5	i) ENZOGENOL™	5 ± 2 mg
	ii) shark cartilage	20 – 175 mg
	Taurine	100 ± 50 mg
	Potassium gluconate	70 ± 20 mg
	Thiamine hydrochloride	25 ± 10 mg
10	Yeast	50 ± 20 mg
	Dextrose (as a tableting agent)	
	Vitamin mix (see example 1a)	optional

This composition can provide some additional benefit for cats. Taurine, an essential dietary ingredient in cats, is fundamental in preventing heart and eye disease. Taurine is also an important part of bile in the cat's digestive system. Potassium Gluconate helps prevent hypocalcaemia, a common diet related deficiency in cats.

Thiamine helps prevent diseases related to thiamine deficiency such as diarrhoea, kidney disease and polioencephomalacia. Yeast provides a rich source of B vitamins and other natural products. Dextrose is included as a tableting agent, instead of the more commonly used lactose, because many cats are lactose intolerant.

Suggested once daily dosage

2.5 kg	1 tablets
> 2.5 kg	2 tablets

Can be administered directly into the mouth or added to the food.

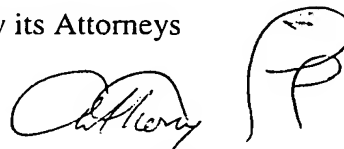
It is also possible to use the compositions of examples 1 through 5 for cats.

● 500630

Aspects of the present invention have been described by way of example only and it should be appreciated that modifications and additions may be made thereto without departing from the scope thereof.

Bomae Laboratories Limited

by its Attorneys


JAMES & WELLS

